

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
	Morphine Sulfate Extended-Release (Narcotic Analgesic – Rx) Capsule: 30 mg, 60 mg, 90 mg, 120 mg	Once-a-day dosing. Total daily dose depends on patient's tolerance and reaction to medication.	
	Injection (as dexamethasone sodium phosphate): EQ 4 mg phosphate/mL, EQ 10 mg phosphate/mL, EQ 20 mg phosphate/mL		
Vincasar PFS	Vincristine Sulfate (Antineoplastic – Rx) Injection: 1 mg/mL	Administer 1.4 mg/m ² IV over 1 minute at weekly intervals	L/A per OPDRA
Fludara	Fludarabine Phosphate (Antineoplastic – Rx) Lyophilized Powder for Reconstitution: 50 mg	25 mg/m ² IV over a period of ~30 minutes daily for 5 consecutive days.	S/A per OPDRA
Lindane	Gamma Benzene Hexachloride (Scabicides/Pediculicides – Rx) Lotion: 1% Shampoo: 1%	Lotion: Apply and leave on for 8 to 12 hours. Shampoo: Apply and leave in hair for 4 minutes.	L/A per OPDRA

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Studies were conducted within FDA for the proposed proprietary names to determine the degree of confusion of “_____” and with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 115 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. An OPDRA staff member wrote one inpatient prescription and one outpatient prescription, each consisting of a combination of marketed and unapproved drug products and prescriptions for “_____” (see below). These written prescriptions were optically scanned and one prescription was delivered via e-mail to each study participant. In addition, one OPDRA staff member recorded a verbal outpatient prescription for each name that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via e-mail.

BEST POSSIBLE COPY

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
---------------------------	---------------------

Inpatient: 30 mg po qd	Outpatient: 30 mg
Outpatient: 30 mg	Take 1 capsule by mouth once a day.
Sig: i cap po QD	#30
#30	

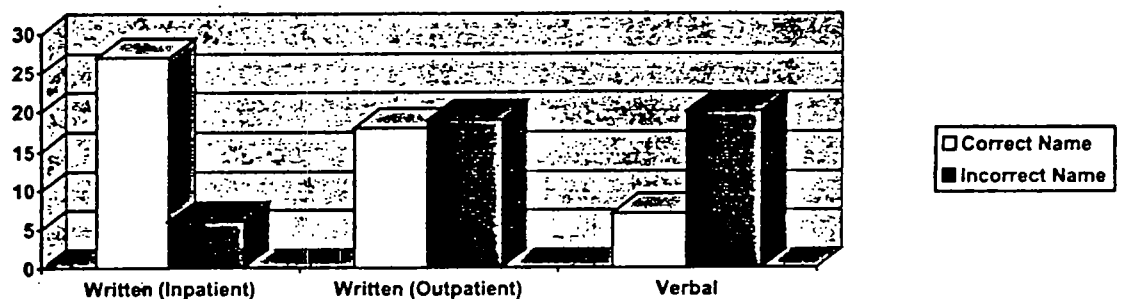
HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Inpatient: 60 mg po Qd prn	Outpatient: 60 mg
Outpatient: 60 mg	Take 1 capsule by mouth once daily.
i cap po qd	#60
#60	

2. Results:

Results of these exercises are summarized below:

Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written: Inpatient	38	33 (87%)	27 (82%)	6 (18%)
Outpatient	39	37 (95%)	18 (49%)	19 (51%)
Verbal: Outpatient	38	27 (71%)	7 (26%)	20 (74%)
Total	115	97 (84%)	52 (54%)	45 (46%)

Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written: Inpatient	39	33 (85%)	11 (33%)	22 (67%)
Outpatient	38	25 (66%)	1 (4%)	24 (96%)
Verbal: Outpatient	38	29 (76%)	7 (24%)	22 (76%)
Total	115	87 (76%)	19 (22%)	68 (78%)



Among the written inpatient prescriptions, 6 (18%) out of 33 respondents interpreted incorrectly. Interpretations included *Evador* and *Zyador*.

Hexadrol is a dexamethasone elixir and is indicated for a variety of diseases such as endocrine, dermatologic, and rheumatic disorders. *Hexadrol* sounds similar to "_____ " due to the "exa" sound. However, *Hexadrol* was supplied as an elixir (0.5 mg/5 mL), tablet (1.5 mg, 4 mg), and injection (EQ 4 mg phosphate/mL and EQ 10 mg phosphate/mL) while "_____ " is supplied in capsule form (30 mg, 60 mg, 90 mg, and 120 mg). They have different dosage forms, different strengths, different route of administration, and different doses. Also, according to the manufacturer, Organon, *Hexadrol* is no longer being manufactured even though the drug is still listed in references such as Facts and Comparisons and the Orange Book. These differences and the fact that *Hexadrol* is no longer being manufactured would decrease the risk of a medication error occurring between these two products.

Exelon is the proprietary name for rivastigmine tartrate. It is indicated for the treatment of mild-to-moderate Alzheimer's dementia. Even though *Exelon* does not sound like "_____", *Exelon* does look like "_____" when scripted (see below). Both drug products have the same dosage form (capsule) and the route of administration (oral). *Exelon* is usually given twice a day while "_____" is given once daily. Even though these two drug products have different directions of use, the prescriber can give the directions as "Use as directed". There are no overlapping strengths, but there are overlapping numbers in the strengths supplied. *Exelon* can be written as "Exelon 3.0 mg" with a trailing zero which may look similar to "_____ 30 mg" if the decimal point in the "3.0" is not seen. Even though "_____" is a controlled substance, prescribers may not always write the prescription on a designated CII prescription pad. According to the verbal portion of the OPDRA study, two (5%) out of thirty-seven respondents interpreted "_____" as *Exelon*. Another respondent also commented that "_____" resembled *Exelon*. Even though the sample size used in the OPDRA study was small, a positive finding from a small sample size signals a higher risk of medication errors when applied to the general population of healthcare workers. If *Exelon* was mistakenly dispensed instead of "_____", then the patient's pain condition would not be controlled. Also, if the patient is on any anticholinergic medications, *Exelon* may interfere with those medications since *Exelon* is a cholinesterase inhibitor. The patient would also be exposed to unnecessary side effects such as nausea, urinary obstruction, and bradycardia. If "_____" was mistakenly dispensed instead of *Exelon* and the instruction was "Take 3.0 mg twice a day" where the 3.0 mg was mistaken as 30 mg, then the patient would receive an overdose of "_____" since "_____" is only taken once daily. The patient's dementia would not be controlled. then the patient's pain condition would not be controlled. Also, if the patient is on any anticholinergic medications, *Exelon* may interfere with those medications since *Exelon* is a cholinesterase inhibitor. The patient would also be exposed to unnecessary side effects such as nausea, urinary obstruction, and bradycardia

Writing Sample:

Exador 30 mg

30mg Exelon 3.0mg

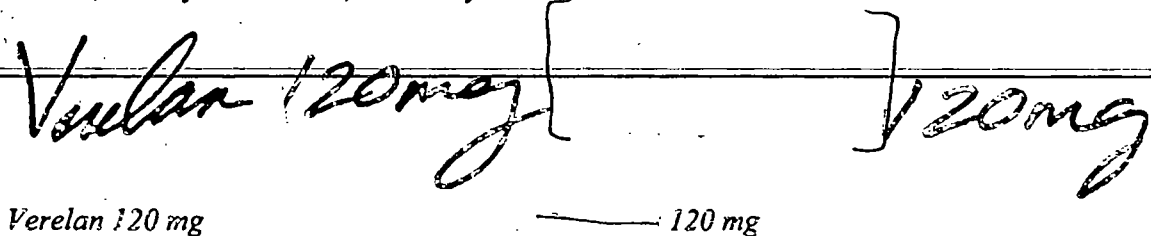
Exelon 3.0 mg

One respondent commented that "_____" reminded her of the drug *Theo-Dur* even though the respondent interpreted the proprietary drug name correctly. *Theo-Dur* is brand name for theophylline and is indicated for the symptomatic relief or prevention of bronchial asthma and reversible bronchospasm associated with chronic bronchitis and emphysema. This drug product

strengths of _____, it would be less likely for _____ to be confused with *Vicodin* when prescribed.

One respondent from the written outpatient prescription portion of the OPDRA study interpreted _____ as *Virilan*, which looks similar to *Virilon* (methyltestosterone) and *Verelan* (verapamil hydrochloride). *Virilon* is used for postpartum breast pain and engorgement, androgen deficiency, postpubertal cryptorchidism, hypogonadism, and male climacteric and impotence. *Virilon* is available as a 10-mg capsule. Methyltestosterone is also available in 10 mg and 25 mg tablets. *Virilon* and " _____" may seem similar when scripted in a certain way. These products do have the same dosage form and the same route of administration. However, _____ is available as a 30-mg, 60-mg, 90-mg, and 120-mg strength. Due to the multiple strengths of _____, it would be less likely for _____ to be confused with *Virilon* when prescribed. Also, according to the database provided by Thomson & Thomson's SAEGIS™ Online Service, the last recorded sales of *Virilon* was 1999. According to Star Pharmaceuticals, *Virilon* is still on the market, but is on back order for 6 months.

Verelan (verapamil hydrochloride) is indicated for the management of essential hypertension. This drug product is available as a 120-mg, 180-mg, 240-mg, and 360-mg capsule. The verapamil hydrochloride is also available as *Verelan PM*, which comes in a 100-mg, 200-mg, and 300-mg capsule. The usual daily dose of *Verelan* is 240 mg once a day, though initial doses of 120 mg a day may be given to patients who have an increased response to verapamil. _____ is also available as a 30-mg, 60-mg, 90-mg, and 120-mg capsule and is administered once a day. Both *Verelan* and _____ share the same route of administration (oral), the same dosage form (capsule), the same dosing schedule (once a day), and also have one strength in common (120 mg). Regarding to the sound-alike and look-alike qualities of the proprietary names, *Verelan* and _____ do not sound alike, but they do look similar when scripted. (See below for sample writing.) Even though _____ is a controlled substance, prescribers may not always write the prescription on a designated CII prescription pad. If *Verelan* was dispensed instead of _____ the patient's pain condition would not be controlled. Also, the patient would experience a decrease in blood pressure resulting in hypotension. Other adverse reactions the patient may unnecessarily be exposed to includes dizziness, constipation, headaches, and lethargy. If _____ was dispensed instead of *Verelan*, then the patient's hypertension may not be properly controlled. The patient would also be exposed to unnecessary side effects such as nausea, urinary obstruction, and bradycardia.



The image shows a handwritten comparison of two prescriptions. On the left, 'Verelan 120mg' is written in a cursive script. To its right, a bracketed section contains another cursive script that reads '120mg'. Below the bracketed section, the text '120 mg' is printed in a standard font.

Verelan 120 mg

_____ 120 mg

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

Please refer to OPDRA Consult 01-0029.

BEST POSSIBLE COPY

In the written inpatient prescription portion of the OPDRA study, one respondent interpreted _____ as *Vicodin*. *Vicodin* is a combination drug product that contains acetaminophen and hydrocodone bitartrate and, like _____, is also a narcotic analgesic. There are similarities between the two proprietary drug names when scripted in a certain way, but the "co" in *Vicodin* and the "ara" in _____ may be enough to distinguish the two names. Both drug products are available in capsule form and have the same route of administration (oral). Also, there are no overlapping strengths between them. There is 500 mg of acetaminophen and 5 mg of hydrocodone bitartrate in *Vicodin* (750 mg/7.5 mg in *Vicodin ES* and 660 mg/10 mg in *Vicodin HP*) while _____ is available in 30 mg, 60 mg, 90 mg, and 120 mg. Due to the multiple strengths of _____, it would be less likely for _____ to be confused with *Vicodin* when prescribed.

One respondent from the written outpatient prescription portion of the OPDRA study interpreted _____ as *Virilan*, which looks similar to *Virilon* (methyltestosterone) and *Verelan* (verapamil hydrochloride). *Virilon* is used for postpartum breast pain and engorgement, androgen deficiency, postpubertal cryptorchidism, hypogonadism, and male climacteric and impotence. *Virilon* is available as a 10-mg capsule. Methyltestosterone is also available in 10 mg and 25 mg tablets. *Virilon* and _____ may seem similar when scripted in a certain way. These products do have the same dosage form and the same route of administration. However, _____ is available as a 30-mg, 60-mg, 90-mg, and 120-mg strength. Due to the multiple strengths of _____, it would be less likely for _____ to be confused with *Virilon* when prescribed. Also, according to the database provided by Thomson & Thomson's SAEGIS™ Online Service, the last recorded sales of *Virilon* was 1999. According to Star Pharmaceuticals, *Virilon* is still on the market, but is on back order for 6 months.

Verelan (verapamil hydrochloride) is indicated for the management of essential hypertension. This drug product is available as a 120-mg, 180-mg, 240-mg, and 360-mg capsule. The verapamil hydrochloride is also available as *Verelan PM*, which comes in a 100-mg, 200-mg, and 300-mg capsule. The usual daily dose of *Verelan* is 240 mg once a day, though initial doses of 120 mg a day may be given to patients who have an increased response to verapamil. _____ is also available as a 30-mg, 60-mg, 90-mg, and 120-mg capsule and is administered once a day. Both *Verelan* and _____ share the same route of administration (oral), the same dosage form (capsule), the same dosing schedule (once a day), and also have one strength in common (120 mg). Regarding to the sound-alike and look-alike qualities of the proprietary names, *Verelan* and _____ do not sound alike, but they do look similar when scripted. (See below for sample writing.) Even though _____ is a controlled substance, prescribers may not always write the prescription on a designated CII prescription pad. If *Verelan* was dispensed instead of _____, the patient's pain condition would not be controlled. Also, the patient would experience a decrease in blood pressure resulting in hypotension. Other adverse reactions the patient may unnecessarily be exposed to includes dizziness, constipation, headaches, and lethargy. If _____ was dispensed instead of *Verelan*, then the patient's hypertension may not be properly controlled. The patient would also be exposed to unnecessary side effects such as nausea, urinary obstruction, and bradycardia.

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

Verelan 120mg [] 120mg

Verelan 120 mg

_____ 120 mg

V. RECOMMENDATIONS:

OPDRA does not recommend the use of the proprietary names _____ and _____

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, R.Ph. at 301-827-3231.

Jennifer Fan, Pharm.D.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

**APPEARS THIS WAY
ON ORIGINAL**



NDA 21-260

DISCIPLINE REVIEW LETTER

Elan Pharmaceuticals
1300 Gould Drive
Gainesville, GA 30504

Attention: Sharon Hamm, Pharm.D.
Senior Vice President, R&D Technical Operations

Dear Dr. Hamm:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for morphine sulfate ———— extended release capsules.

We also refer to your submissions dated February 21 and March 5, 2001. The submissions contain information related to use of the brand names "Avinza" and ————.

The Office of Post Marketing Drug Risk Assessment (OPDRA) has completed review of the information, and we have the following comments.

1. OPDRA refers the applicant to a July 2000 article in Pharmaceutical Executive by Jerry Phillips.

Today, CDER's Office of Post-marketing Drug Risk Assessment (OPDRA) is responsible for the pre- and post-marketing assessment of medication errors resulting from nomenclature, labeling and packaging of drug products. The medication error staff is comprised of ten clinical pharmacists and a physician.

Since October 1999, OPDRA has reviewed approximately four hundred proposed proprietary names for unapproved drug products. Under the new OPDRA process, proprietary names undergo a multifactorial review using the following systems approach that was designed to improve consistency and minimize risk with sound-alike and look-alike names.

**APPEARS THIS WAY
ON ORIGINAL**

a. Expert Panel Review

An Expert Panel meets weekly to exchange opinions on the safety of the proprietary name. The panel is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising and Communications (DDMAC) who rely on their clinical, regulatory, and professional experiences when making a decision on the acceptability of a proprietary name.

b. Handwriting Analysis and Verbal Analysis

These analysis are conducted within FDA, to determine the degree of confusion of the proposed proprietary name with other U.S. drug names due to similarity in the visual appearance and/or verbal pronunciation of the drug name. FDA health care professionals (nurses, pharmacists, and physicians) are requested to interpret both written inpatient orders and outpatient prescriptions and verbal orders in an attempt to simulate the prescription ordering process with handwritten and verbal prescriptions.

c. Computer-Assisted Analysis

Currently OPDRA utilizes existing FDA databases to identify potential sound-alike and/or look-alike similarity of proprietary names. In the future, OPDRA plans to use validated computer software that will improve the ability to detect orthographic (spelling) or phonological (sound) similarities in proprietary names.

d. Labeling and Packaging Analysis

OPDRA provides a safety assessment of the container labels, carton and package insert labeling, and proposed packaging of each product to identify areas of improvement that might minimize potential user error.

e. Overall Risk Evaluation

The final phase of the name review process involves an overall risk analysis that weighs the results of each phase and additional risk factors such as overlapping strengths, dosage forms, dosing recommendations, indications for use, storage, labeling, and packaging, and important lessons learned from the Agency's post-marketing experience.

**APPEARS THIS WAY
ON ORIGINAL**

f. Role of the reviewing divisions

The Office of Review Management's 15 divisions and the office of Generic Drugs continue to be the point of contact and source of primary regulatory decisions on proprietary matters. OPDRA will provide uniform consultative safety risk assessment and make recommendations, but the primary decision on the suitability of proprietary names rests with the responsible reviewing division or Office of Drug Evaluation director, as appropriate.

2. _____ submitted the list of the *eighteen approved drug names*, which were referred to in the Sponsor's comments (see above). OPDRA reviewed the list of names and concluded the following:

- Six drug name consults were reviewed by the Labeling and Nomenclature Committee (LNC), not by OPDRA.
- Nine drug name consults reviewed by OPDRA did not contain a _____ review (Sponsor did not submit _____ review).
- One drug name consult, which did include a _____ review, was rejected by OPDRA.
Subsequently, the Sponsor submitted a new name.
- One drug name consult, which did include a _____ review, was originally objected to, however, subsequent findings reversed the objection.
- One drug name consult was not reviewed by either OPDRA or LNC.

OPDRA is in the process of establishing sample size guidelines and is not prepared to comment at this time. Test subjects should be representative of the user population to evaluate potential for confusion and medication error. In regards to the sample size utilized by _____ in the evaluation of the proprietary name "Avinza", OPDRA did not question the appropriateness of the sample size but rather the results obtained from the sample size. A 3% potential for confusion in such a small sample size may indicate a significant risk when extrapolated to the general U.S. population. Unlike the management of an adverse reaction, where the acceptable level of risk is always weighed against its benefits for the indicated use, there is no acceptable level of risk when we manage a medication error. Medication errors are preventable events that can be minimized by implementing many different measures such as differentiating product packaging, the use of barcodes in medication administration, computerized prescription order entry, etc. OPDRA takes a proactive stance against medication errors in that a decision for a proprietary name change is not based solely on the total number of reported cases and serious patient outcome, but also the *potential* to cause an error and *potential* to cause patient harm.

APPEARS THIS WAY
ON ORIGINAL

3. _____ study resulted in a 3% probability of confusion due to a "sound-alike" similarity and a 1% probability of confusion due to "look-alike" similarity between Avinza and Evista. Although there are limitations to the predicative value of these studies primarily due to sample size, a positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population.

_____ conducted a confirmatory market research between Avinza and the drug names (Avinar, Avail, Avita, Relenza, and Evista) listed with the original _____ review. One hundred sixty nine (169) *medical professionals* were shown the *profiles* for each of the five drugs listed and asked whether or not a dispensing error would occur between the test drug Avinza and the currently marketed drug. The results are as follows:

"WOULD A DISPENSING ERROR OCCUR WITH AVINZA?"		
Drug Name	No	Yes
Avinar	169	0
Avail	168	1
Avita	168	1
Relenza	167	2
Evista	166	3

Two percent of the respondents (3/166) indicated that there is a possibility of confusion between Avinza and Evista even though they were shown the *profiles for all* the drugs. Two percent in such a small sample size can translate into thousands of errors when extrapolated to the U.S. population. OPDRA believes the similarity in look-alike and sound-alike potential poses a significant risk to the public.

OPDRA focuses on reducing the potential for medication errors associated with look-alike and sound-alike names by examining the results from the handwriting and verbal analysis studies, Expert Panel review, and computer-assisted analysis.

OPDRA provides an overall benefit-to-risk analysis of a proposed proprietary name by considering numerous risk factors. These factors include overlapping strengths, dosage forms, dosing recommendations, use and indications, storage, labeling and packaging.

OPDRA reviewing process does not utilize a scaling process of assigning weight to confounding factors. Although OPDRA considers differences in drug class, indication, dosage form, route of administration, strength, dosage frequency, dispensing environment, and controlled substance category in the evaluation of confusion potential, post-marketing experience has demonstrated medication errors occurring even though these factors are present to eliminate the potential for confusion. Some examples include the following:

BEST POSSIBLE COPY

Post-marketing experience with the drug product "Celebrex" has demonstrated that having *noteworthy differences* between products *does not eliminate* the potential for error, as the Agency has received 116 reported cases of medication errors involving Celebrex, Celexa, and Cerebyx. Celebrex is an NSAID, cox-2 inhibitor indicated for the relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis. Celexa is a serotonin reuptake inhibitor indicated for the treatment of depression. Cerebyx is a prodrug and its active metabolite is phenytoin. Table 1 describes the FDA approved dosage forms, strengths and usual dosages of each product. Celebrex and Cerebyx share none of the common factors mentioned above and therefore one would perceive that these three drug products would never be confused. Also, the only commonality that Celebrex and Celexa share is a dosing interval of once daily. The only *common factor* that these names share is the *sound-alike and look-alike properties of their names*.

TABLE 1

NAME OF DRUG	Available Strength and Dosage Form	Usual Dosage
Celebrex	100 mg and 200 mg Capsules	200 mg once daily or 100 mg to 200 mg twice daily
Cerebyx-	50 mg PE/mL Injection 10 mL and 2 mL vial	Varies depending on indication. Average of 10-20 mg PE/kg
Celexa	20 mg and 40 mg Tablets	20 mg to 40 mg once daily. Up to 60 mg daily

Therefore, based on previous post-marketing experience, OPDRA does not believe that differences such as differentiating dosage forms, different routes of administration, different doses and different indications rule out any potential for confusion when the names clearly sound or look alike to a currently marketed drug product. What makes Celebrex unique is that the errors are *not* overwhelmingly related to other confounding factors such as illegible handwriting, overlapping indications for use, overlapping strengths, mispronunciation of the product names, similar prescribing environments but rather to a cognitive error. It is evident from the case reports that the sound-alike/look-alike properties of the name alone are not the source of confusion in the minds of health care providers. The reports describe health care providers thinking, seeing, and hearing one product name but prescribing, transcribing, and dispensing another. There are numerous case reports that describe prescriptions being written correctly, typed correctly, but filled incorrectly on initial fills as well as product refills. Also, physicians have reported of thinking of one drug product but prescribing another. These errors cannot be written off as mere incompetence because the same errors are occurring to numerous individuals on a large scale.

BEST POSSIBLE COPY

Post-marketing experience has demonstrated errors occurring between Class II controlled substances and non-scheduled drug products. Such examples include:

Inderal	Adderall
Demerol	Desyrel
Codeine	Iodine
Codeine	Cardene
Codeine	Lodine
OxyContin	Oxybutynin

4. _____ states that a look-alike and sound-alike similarity does exist between Avinza and the drug products OPDRA cited (Albenza, Alfenta, Evista, and Aventyl). Additionally, _____ also stated that a "real life prescribing/dispensing environment" will not allow a potential for confusion or error to take place. Although there is some validity to this perspective, _____ neglected to examine this situation from a broader perspective.
- Class II controlled substance prescriptions- verbal orders for Class II controlled substances are possible, in that physicians routinely ask nurses to administer controlled substances from narcotic cabinets and the Pyxis.
 - Some new practitioners are not aware of the fact that verbal Class II controlled substances are not permitted by state law. Often new practitioners attempt to provide verbal orders over the phone not realizing that verbal Class II controlled substance prescriptions are not permitted. If and when an uninformed physician phones a prescription, the pharmacist may fill the prescription for Evista or Albenza rather than Avinza, knowing that verbal Class II controlled substance prescriptions are not permitted by law.
 - Some physicians also include refills on Class II controlled substance prescriptions, unaware of the fact that these prescriptions are not allowed by to be refilled by law.
 - ~~Although Class II controlled substances are stored in secured and supervised environments, secured and supervised environments do not prohibit a pharmacist from filling a prescription for something other than Avinza, especially when that pharmacist perceives the drug to be for something other than Avinza.~~

Post-marketing experience has demonstrated errors occurring between Class II controlled substances and non-scheduled drug products. Such examples include:

Inderal	Adderall
Demerol	Desyrel
Codeine	Iodine
Codeine	Cardene
Codeine	Lodine
OxyContin	Oxybutynin

BEST POSSIBLE COPY

Evista

Evista and Avinza share an overlapping dosage form, solid oral dosage form, route of administration, strength, frequency, dispensing environment and have sound-alike and look-alike potential. The _____ concluded that 3 out of 166 medical professionals (2%) indicated a potential for error between Avinza and Evista does exist. This result indicates a significant risk when extrapolated to the general U.S. population. In regards to the Sponsor's efforts to distinguish the dispensing environment and practice for a Class II Controlled Substance, post-marketing experience has demonstrated that cognitive errors are also responsible for medication errors (i.e., two drugs having look-alike or sound-alike potential with no other commonalities may cause prescribing or dispensing errors). Post-marketing experience has also demonstrated that medication errors occur with drugs that have minute look-alike and sound-alike potential but share other characteristics such as strength, dosing schedule, dosage form and route of administration. Examples of this include:

Table 2

Navane (thiothixene)	Norvasc (amlodipine)
Celebrex (celecoxib)	Celexa (citalopram)
Prozac (fluoxetine)	Prilosec (omeprazole)

The risks associated with the inadvertent dispensing of Evista for Avinza include all side effects and adverse events related to hormonal supplements. The risks associated with the inadvertent dispensing of Avinza for Evista include all side effects and adverse events related to central nervous depression.

Albenza

Not only do Albenza and Avinza sound similar, the drug names look similar when scripted (see writing sample below). The _____ review also indicated that because "Albenza is an orphan drug, it has a highly specific and limited indication that typically renders it unavailable in common pharmacy stock". Although this may be true for some situations, it does not represent all institutions and all patients who are treated with the drug. The goal of medication error prevention is to apply standards of expectations that attempt to work in all situations, not just the majority. Otherwise, the assumption is that it is acceptable to have a risk of medication errors occurring in those facilities that fall into the minority. In addition, post-marketing experience has demonstrated that even drug products with a single strength (similar to Albenza) have the potential of confusion with drug products that are available in multiple strengths. One recent example of this is Sarafem.

BEST POSSIBLE COPY

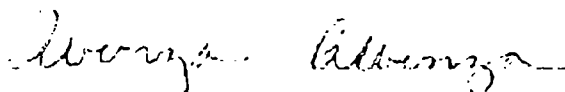
Sarafem was approved on February 1st 2001. Since the launch of this product the Agency has received four medication error reports of name confusion between Sarafem and Serophene. Sarafem is the proprietary name for fluoxetine and is indicated for the treatment of premenstrual dysphoric disorder (PMDD). Serophene is an ovulation stimulant sex hormone. The available dosage forms and usual dosages are as follows:

Product Name	Dosage Form and Strength	Usual Dosage
Sarafem	Capsules, 10 mg, 20 mg	10-20 mg daily for up to 6 months
Serophene	Tablets, 50 mg	50-100 mg daily for 5 days

After comparing the product profiles of these two drug products one would believe that there would be no confusion between the two products. However, the fact that Sarafem has a single strength associated with it increases the chance that prescribers would not include this information on the prescription and thus increases the risk of confusion.

AVINZA

ALBENZA



The outcomes associated with the inadvertent confusion of Avinza and Albenza may be life threatening. Fatalities associated with the use of Albenza have been reported due to granulocytopenia and pancytopenia, which results from harm inflicted to the liver and bone marrow. Additionally, acute renal failure related to Albenza therapy has been observed. A patient that receives Avinza in place of Albenza, may experience respiratory depression and the possibility of an allergic reaction if the patients is hypersensitive to morphine.

Aventyl

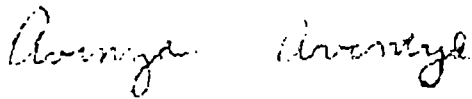
The analysis conducted by _____ also stated that "differences in letters beyond the first syllable would unquestionably distinguish these names for both verbal and written prescriptions". OPDRA directs you to Table 1 and ask you to apply this assumption to the drug names, which have caused medication errors. Most of the names have differences in letters beyond the *first letter* and not the first syllable that "would unquestionably distinguish these names for both verbal and written prescription." _____ also indicated that Aventyl (or the medication nortriptyline HCl) is prescribed with decreasing frequency given the greater accessibility of selective serotonin reuptake inhibitors (SSRI's) for treating mood disorders. After conducting a search on Thomson and Thomson's database for trademarks and domain names, Aventyl was found to have a high sales indicator meaning that the drug is still widely used. In addition, _____ stated that

BEST POSSIBLE COPY

Aventyl may be ordered by its generic name or by one of its better known brand names, Pamelor. This statement is based on an assumption and not "real-life" prescribing practices. More and more generic manufacturers are assigning proprietary names to their products so that physicians distinctly choose their products by proprietary name when prescribing instead of leaving it up to the pharmacist to substitute. Although Aventyl and Avinza do not sound similar, the drug names look similar (see writing sample below). In addition, these drug products share similar dosage forms. Although nortriptyline has been administered in up to 4 divided doses throughout the day, *it is long-acting and the entire daily dose may be administered as a once daily dose (see script below writing sample).*

AVINZA

AVENTYL



Avinza 30 mg Disp: #30 Sig: 1 po QD as directed	Aventyl 30 mg Disp: 30 days supply Sig: 30 mg QD as directed
---	--

If Avinza is inadvertently dispensed in place of Aventyl, a patient may experience side effects related to central nervous depression. If Aventyl is inadvertently dispensed in place of Avinza, a patient may remain untreated for moderate to severe pain as well as experience side effects associated with Aventyl.

Alfenta

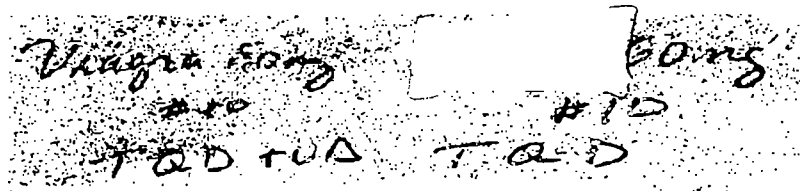
Although Alfenta and Avinza are both categorized as Class II controlled substances, differences in dosing, administration, dosage form and a lack of convincing look-alike and sound-alike potential render minimal confusion between the two drug products. As noted by _____, Alfenta is an adjunct for anesthesia that is administered intravenously only by qualified personnel in an appropriately equipped medical setting and not available by prescription to any patient outside of such settings.

5. OPDRA does not recommend the use of the proprietary name '_____'

In reviewing the proprietary name '_____' the primary concerns raised were related to many sound-alike, look-alike names that already exist in the U.S. marketplace.

BEST POSSIBLE COPY

Although Viagra and ~~Viagra~~ do not sound similar, the names look strikingly similar when scripted (see writing sample below). *Three participants* from the *inpatient and outpatient* study responded with Viagra as an interpretation as another respondent noted the similarity in appearance. ~~Viagra~~ and Viagra share similar dosing frequencies (once daily) and dosage forms. Despite the fact that ~~Viagra~~ and Viagra do not share similar strengths, the potential for confusion is possible in that the strengths (60 mg and 50 mg, respectively) may appear similar when scripted (see writing sample below). Post-marketing experience has demonstrated errors occurring between drugs that share look-alike and sound-alike properties solely. The inadvertent confusion of ~~Viagra~~ for Viagra could cause central nervous depression and/or the possibility of an allergic reaction if the patient is hypersensitive to morphine. The risk associated with the inadvertent confusion of Viagra for ~~Viagra~~ include all side effects and adverse events related to Viagra. Also, the patient will remain untreated for moderate to severe pain.



In, addition, post-marketing experience has demonstrated errors occurring between Class II controlled substances and non-scheduled drug products. Such examples include:

6. ~~Viagra~~ report lacked information that would allow OPDRA to give a fair evaluation of ~~Viagra~~ methodology of the study. Information on key methodological issues was not submitted by ~~Viagra~~ such as the selection of the study sample of physicians and pharmacists, and the validation of the techniques used.

a. Selection of Participating Practitioners

According to the report, the participants were randomly selected across pre-selected geographic areas. However, the information on the process of how participating physicians and pharmacists were selected was not included in ~~Viagra~~'s report. The criteria on the selection process (inclusion and exclusion criteria) and how those criteria were met were not explained.

The sampling frame for the selection of the participants was not given. For example, did the selection of cardiologists arise from a list of professional organizations?

Without the information of the selection and recruitment process the results of this study cannot be interpreted and applied to the universe of practicing physicians and pharmacists in the United States, especially since the study sample was small.

There was no mention of whether or not the participants were reimbursed for their participation in the study. Reimbursement may bias the results of the study.

b. Validation of Methods Used

Information was not presented to demonstrate that the methods used in the study actually work in predicting whether any existing brand/generic names may be confusingly similar to the test name in actual practice.

1) Verbal Prescription Filling

The methodology in the study is very different from an actual practice situation, in an actual practice setting where a very busy environment exists, pharmacists receive the entire prescription over the phone from a prescriber. The drug name is pronounced in the context of an entire prescription. Usually, once the pharmacist listens to all the information, the interpreted prescription is then re-read to the physician and clarifies any necessary information. Such clarification can result in the unveiling of an error in perception of the drug name. The method in the study, where only the name is spoken, is contrived and unrealistic. The result may have been very different had the simulation been more true to actual practice.

2) Scripted Prescription Filling

As in the above comment regarding the Verbal Prescription Filling, the methodology is not clearly described or validated in this portion of the study report. According to —'s report, the physicians scripted the product name, and the script was sent on-line for the pharmacists' interpretation. This method does not simulate actual prescription practice and the results cannot be generalized to an actual practice situation.

3) Orthographic String Similarity Testing

The results have not been validated or related to real outcomes. Nothing is included about the potential severity of outcome that could be associated with a mix up in the list of parameters that are related to patient safety.

4) Use of "positive" and "negative" controls

—'s report stated repeatedly that "positive" and "negative" controls for — were used in several analyses, but it is unclear what it was meant by it. The use of the terms in the analyses presented in this report appears to be incorrect.

5) BRANDTEST —

— completed an additional phase to further evaluate the accuracy of verbal and written similarity between Avinza and Albenza, Alfenta, Aventyl and Evista. The participants (30 oncologists, 10 anesthesiologists, 10 internal medicine specialists and 50 pharmacists) were instructed to listen to a recording of — and/or view a scripted representation of —. The participants reported what they heard or viewed by selecting one name from a list of test drug names one of which was —. Although it was not mentioned how many prescriptions were allocated to each pharmacist, it is highly possible that after the first prescription, the pharmacist would guess the purpose of the study and select the right drug.

Overall, the study conducted by — lacks information to assess the validity of the study. The sample size is too small to detect all the potential drug names at risk for being confused with —.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

**APPEARS THIS WAY
ON ORIGINAL**

NDA 21-260

Page 14

If you have any questions, call Kimberly Compton, Regulatory Project Manager, at (301) 827-7432.

Sincerely,

Cathie Schumaker, R.Ph.
Chief, Project Management Staff
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Cc: Ligand Pharmaceuticals
10275 Science Center Drive
San Diego, CA 92121-1117
Attention: Howard T. Holden, Ph.D.
Vice President, Regulatory Affairs and Compliance

**APPEARS THIS WAY
ON ORIGINAL**

/s/

Cathie Schumaker

3/30/01 11:52:17 AM

APPEARS THIS WAY
ON ORIGINAL

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: ~~March 10, 2001~~

DUE DATE:
March 29, 2001

OPDRA CONSULT #: 00-0264

TO: Cynthia McCormick, MD
Director, Division of Anesthetics, Critical Care, and Addiction Drug Products
HFD-170

THROUGH: Kim Compton, Project Manager
HFD-170

PRODUCT NAME:

~~Avinza~~
(Morphine sulfate Extended-release
Capsules)
30 mg, 60 mg, 90 mg, 120 mg

Manufacturer: Elan Holdings, Inc.
Pharmaceutical Division

NDA #: 21-260

SAFETY EVALUATOR: Alina R. Mahmud, RPh.

SUMMARY: In response to a consult from the Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170), OPDRA reviewed Elan Pharmaceuticals' justification provided for use of the tradename Avinza for this product. Elan Pharmaceuticals contracted with _____; for evaluation of the proprietary name "Avinza" to determine the potential for confusion with the approved proprietary names.

ODRA RECOMMENDATION: OPDRA does not recommend the use of the proprietary name "Avinza".

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

BEST POSSIBLE COPY

**APPEARS THIS WAY
ON ORIGINAL**

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: March 19, 2001

NDA NUMBER: 21-260

NAME OF DRUG: Avinza
(Morphine Sulfate Extended-release Capsules)
30 mg, 60 mg, 90 mg, 120 mg

NDA HOLDER: Elan Holdings, Inc.

I. INTRODUCTION

This consult was written in response to a request from the Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170), for assessment of the tradename "Avinza", regarding potential name confusion with other proprietary/generic drug names. The sponsor contracted with _____ to evaluate the use of the proposed name Avinza.

In the initial review of this name that was completed on November 30, 2000, OPDRA found the name unacceptable because of the potential for confusion with the following approved drug names: Evista, Alfenta, Albenza, and Aventyl.

PRODUCT INFORMATION

Avinza is the proposed proprietary name for morphine sulfate. Avinza is formulated as a once-a-day extended-release capsule that contains both immediate release and extended release beads of morphine sulfate for oral administration. Each Avinza capsule contains 30 mg, 60 mg, 90 mg, or 120 mg of morphine sulfate, USP. Avinza is indicated for the relief of moderate to severe pain and is intended for the use in patients that require repeated dosing with opioid analgesics over periods of more than a few days. Avinza will be available as a capsule in both blister pack cartons and bottles of 30, 100, 250, 500 counts.

II. RESPONSE TO THE SPONSOR'S APPEAL

Administrative Process

Sponsor's comments:

1. OPDRA is a newly established entity within CDER. OPDRA has assumed a task formerly performed by the Labeling and Nomenclature Committee.

Please provide an overview of OPDRA's process to review trade names and how the group interfaces with the review Divisions

OPDRA's response

OPDRA refers the applicant to a July 2000 article in Pharmaceutical Executive by Jerry Phillips.

Today, CDER's Office of Post-marketing Drug Risk Assessment (OPDRA) is responsible for the pre- and post-marketing assessment of medication errors resulting from nomenclature, labeling and packaging of drug products. The medication error staff is comprised of ten clinical pharmacists and a physician.

Since October 1999, OPDRA has reviewed approximately four hundred proposed proprietary names for unapproved drug products. Under the new OPDRA process, proprietary names undergo a multifactorial review using the following systems approach that was designed to improve consistency and minimize risk with sound-alike and look-alike names:

Expert Panel Review

An Expert Panel meets weekly to exchange opinions on the safety of the proprietary name. The panel is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC) who rely on their clinical, regulatory, and professional experiences when making a decision on the acceptability of a proprietary name.

Handwriting Analysis and Verbal Analysis

These analysis are conducted within FDA, to determine the degree of confusion of the proposed proprietary name with other U.S. drug names due to similarity in the visual appearance and/or verbal pronunciation of the drug name. FDA health care professionals (nurses, pharmacists, and physicians) are requested to interpret both written inpatient orders and outpatient prescriptions and verbal orders in an attempt to simulate the prescription ordering process with handwritten and verbal prescriptions.

Computer-Assisted Analysis

Currently OPDRA utilizes existing FDA databases to identify potential sound-alike and/or look-alike similarity of proprietary names. In the future, OPDRA plans to use validated computer software that will improve the ability to detect orthographic (spelling) or phonological (sound) similarities in proprietary names.

Labeling and Packaging Analysis

OPDRA provides a safety assessment of the container labels, carton and package insert labeling, and proposed packaging of each product to identify areas of improvement that might minimize potential user error.

Overall Risk Evaluation

The final phase of the name review process involves an overall risk analysis that weighs the results of each phase and additional risk factors such as overlapping strengths, dosage forms, dosing recommendations, indications for use, storage, labeling, and packaging, and important lessons learned from the Agency's post-marketing experience.

Role of the reviewing divisions:

The Office of Review Management's 15 divisions and the office of Generic Drugs continue to be the point of contact and source of primary regulatory decisions on proprietary matters. OPDRA will provide uniform consultative safety risk assessment and make recommendations, but the primary decision on the suitability of proprietary names rests with the responsible reviewing division or Office of Drug Evaluation director, as appropriate.

Sponsor's comments

2. The Agency's Discipline Review Letter of January 17, 2001, noted that "an epidemiological review of the submitted _____ evaluation of the proprietary name Avinza, indicated a potential name confusion as high as 3% in the _____'s small sample size a higher risk and potential for medication errors when extrapolated to the U.S. population." _____ attests that the sample sizes used in our studies are similar to those used in previously conducted studies of proposed names that have received favorable recommendations from the Agency.

In 2000 and 2001, eighteen proposed names were approved by the Agency that involved testing with _____'s methodology. In sixteen of those instances, the sample size was identical to the sample size utilized in testing Avinza: 100 total respondents comprised of an equal split of pharmacists and appropriate physicians.

Please provide Ligand specific guidance on the appropriate sample size and professional mix, i.e., physicians, pharmacist, to be used in research to evaluate potential for confusion and medication errors.

OPDRA's response

_____ submitted the list of the *eighteen approved drug names*, which were referred to in the Sponsor's comments (see above). OPDRA reviewed the list of names and concluded the following:

- Six drug name consults were reviewed by the Labeling and Nomenclature Committee (LNC), not by OPDRA.
- Nine drug name consults reviewed by OPDRA did not contain a _____ review (Sponsor did not submit _____ review).
- One drug name consult, which did include a _____ review, was rejected by OPDRA. Subsequently, the Sponsor submitted a new name.
- One drug name consult, which did include a _____ review, was originally objected to, however, subsequent findings reversed the objection.
- One drug name consult was not reviewed by either OPDRA or LNC.

OPDRA is in the process of establishing sample size guidelines and is not prepared to comment at this time. Test subjects should be representative of the user population to evaluate potential for confusion and medication error. In regards to the sample size utilized by _____ in the evaluation of the proprietary name "Avinza", OPDRA did not question the appropriateness of the sample size but rather the results obtained from the sample size. A 3% potential for confusion in such a small sample size may indicate a significant risk when extrapolated to the general U.S. population. Unlike the management of an adverse reaction, where the acceptable level of risk is

listed and asked whether or not a dispensing error would occur between the test drug Avinza and the currently marketed drug. The results are as follows:

<u>"WOULD A DISPENSING ERROR OCCUR WITH AVINZA?"</u>		
Drug Name	No	Yes
Avinar	169	0
Avail	168	1
Avita	168	1
Relenza	167	2
Evista	166	3

Two percent of the respondents (3/166) indicated that there is a possibility of confusion between Avinza and Evista even though they were shown the *profiles for all* the drugs. Two percent in such a small sample size can translate into thousands of errors when extrapolated to the U.S. population. OPDRA believes the similarity in look-alike and sound-alike potential poses a significant risk to the public.

- (b) OPDRA focuses on reducing the potential for medication errors associated with look-alike and sound-alike names by examining the results from the handwriting and verbal analysis studies, Expert Panel review, and computer-assisted analysis. OPDRA provides an overall benefit-to-risk analysis of a proposed proprietary name by considering numerous risk factors. These factors include overlapping strengths, dosage forms, dosing recommendations, use and indications, storage, labeling and packaging.
- (c) OPDRA reviewing process does not utilize a scaling process of assigning weight to confounding factors. Although OPDRA considers differences in drug class, indication, dosage form, route of administration, strength, dosage frequency, dispensing environment, and controlled substance category in the evaluation of confusion potential, post-marketing experience has demonstrated medication errors occurring even though these factors are present to eliminate the potential for confusion. Some examples include the following:
 - Post-marketing experience with the drug product "Celebrex" has demonstrated that having *noteworthy differences* between products *does not eliminate* the potential for error, as the Agency has received 116 reported cases of medication errors involving Celebrex, Celexa, and Cerebyx. Celebrex is an NSAID, cox-2 inhibitor indicated for the relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis. Celexa is a serotonin reuptake inhibitor indicated for the treatment of depression. Cerebyx is a prodrug and its active metabolite is phenytoin. Table 1 describes the FDA approved dosage forms, strengths and usual dosages of each product. Celebrex and Cerebyx share none of the common factors mentioned above and therefore one would perceive that these three drug products would never be confused. Also, the only commonality that Celebrex and Celexa share is a dosing interval of once daily. The only *common factor* that these names share is the *sound-alike and look-alike properties of their names*.

TABLE 1

NAME OF DRUG	Available Strength and Dosage Form	Usual Dosage
Celebrex	100 mg and 200 mg Capsules	200 mg once daily or 100 mg to 200 mg twice daily
Cerebyx	50 mg PE/mL Injection 10 mL and 2 mL vial	Varies depending on indication. Average of 10-20 mg PE/kg
Celexa	20 mg and 40 mg Tablets	20 mg to 40 mg once daily. Up to 60 mg daily

Therefore, based on previous post-marketing experience, OPDRA does not believe that differences such as differentiating dosage forms, different routes of administration, different doses and different indications rule out any potential for confusion when the names clearly sound or look alike to a currently marketed drug product. What makes ~~these~~ unique is that the errors are *not* overwhelmingly related to other confounding factors such as illegible handwriting, overlapping indications for use, overlapping strengths, mispronunciation of the product names, similar prescribing environments but rather to a cognitive error. It is evident from the case reports that the sound-alike/look-alike properties of the name alone are not the source of confusion in the minds of health care providers. The reports describe health care providers thinking, seeing, and hearing one product name but prescribing, transcribing, and dispensing another. There are numerous case reports that describe prescriptions being written correctly, typed correctly, but filled incorrectly on initial fills as well as product refills. Also, physicians have reported of thinking of one drug product but prescribing another. These errors cannot be written off as mere incompetence because the same errors are occurring to numerous individuals on a large scale.

- Post-marketing experience has demonstrated errors occurring between Class II controlled substances and non-scheduled drug products. Such examples include:

Inderal	Adderall
Demerol	Desyre
Codeine	Iodine
Codeine	Cardene
Codeine	Lodine
OxyContin	Oxybutynin

Agency Concerns

Sponsor's comments

4. The Agency disclosed that the following drug product names are of major concern to OPDRA:

Look-alike confusion potential (when scripted, written in cursive): Albenza and Alfenta

Look-alike and sound-alike confusion potential: Evista and Aventyl

A response to the Agency's concerns was contained in the aforementioned submission of February 9, 2001 (Attachment 1). The response included an analysis of product profiles (indication,

Not only does Albenza and Avinza sound similar, the drug names look similar when scripted (see writing sample below). The _____ review also indicated that because "Albenza is an orphan drug, it has a highly specific and limited indication that typically renders it unavailable in common pharmacy stock". Although this may be true for some situations, it does not represent all institutions and all patients who are treated with the drug. The goal of medication error prevention is to apply standards of expectations that attempt to work in all situations, not just the majority. Otherwise, the assumption is that it is acceptable to have a risk of medication errors occurring in those facilities that fall into the minority. In addition, post-marketing experience has demonstrated that even drug products with a single strength (similar to Albenza) have the potential of confusion with drug products that are available in multiple strengths. One recent example of this is Sarafem.

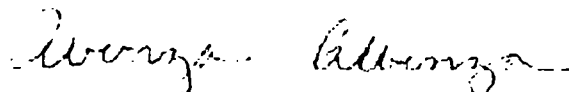
Sarafem was approved on February 1st 2001. Since the launch of this product the Agency has received four medication error reports of name confusion between Sarafem and Serophene. Sarafem is the proprietary name for fluoxetine and is indicated for the treatment of premenstrual dysphoric disorder (PMDD). Serophene is an ovulation stimulant sex hormone. The available dosage forms and usual dosages are as follows:

Product Name	Dosage Form and Strength	Usual Dosage
Sarafem	Capsules, 10 mg, 20 mg	10-20 mg daily for up to 6 months
Serophene	Tablets, 50 mg	50-100 mg daily for 5 days

After comparing the product profiles of these two drug products one would believe that there would be no confusion between the two products. However, the fact that Sarafem has a single strength associated with it increases the chance that prescribers would not include this information on the prescription and thus increases the risk of confusion.

AVINZA

ALBENZA



The image shows two handwritten drug names in cursive script. The first name is 'Avinza' and the second name is 'Albenza'. The two names are written side-by-side, demonstrating their visual similarity when scripted.

The outcomes associated with the inadvertent confusion of Avinza and Albenza may be life-threatening. Fatalities associated with the use of Albenza have been reported due to granulocytopenia and pancytopenia, which results from harm inflicted to the liver and bone marrow. Additionally, acute renal failure related to Albenza therapy has been observed. A patient that receives Avinza in place of Albenza, may experience respiratory depression and the possibility of an allergic reaction if the patients is hypersensitive to morphine.

Aventyl

BEST POSSIBLE COPY

The analysis conducted by _____ also stated that "differences in letters beyond the first syllable would unquestionably distinguish these names for both verbal and written prescriptions". OPDRA directs you to Table 1 and ask you to apply this assumption to the drug names, which have caused medication errors. Most of the names have differences in letters beyond the *first letter*

and not the first syllable that “would unquestionably distinguish these names for both verbal and written prescription.” _____ also indicated that Aventyl (or the medication nortriptyline HCl) is prescribed with decreasing frequency given the greater accessibility of selective serotonin reuptake inhibitors (SSRI’s) for treating mood disorders. After conducting a search on Thomson and Thomson’s database for trademarks and domain names, Aventyl was found to have a high sales indicator meaning that the drug is still widely used. In addition, _____ stated that Aventyl may be ordered by its generic name or by one of its better known brand names, Pamelor. This statement is based on an assumption and not “real-life” prescribing practices. More and more generic manufacturers are assigning proprietary names to their products so that physicians distinctly choose their products by proprietary name when prescribing instead of leaving it up to the pharmacist to substitute. Although Aventyl and Avinza do not sound similar, the drug names look similar (see writing sample below). In addition, these drug products share similar dosage forms. Although nortriptyline has been administered in up to 4 divided doses throughout the day, *it is long-acting and the entire daily dose may be administered as a once daily dose (see script below writing sample).*

AVINZA

AVENTYL

Avinza Aventyl

<p>Avinza 30 mg Disp: #30 Sig: 1 po QD as directed</p>	<p>Aventyl 30 mg Disp: 30 days supply Sig: 30 mg QD as directed</p>
--	---

If Avinza is inadvertently dispensed in place of Aventyl, a patient may experience side effects related to central nervous depression. If Aventyl is inadvertently dispensed in place of Avinza, a patient may remained untreated for moderate to severe pain as well as experience side effects associated with Aventyl.

Alfenta

Although Alfenta and Avinza are both categorized as Class II controlled substances, differences in dosing, administration, dosage form and a lack of convincing look-alike and sound-alike potential render minimal confusion between the two drug products. As noted by _____ Alfenta is an adjunct for anesthesia that is administered intravenously only by qualified personnel in an appropriately equipped medical setting and not available by prescription to any patient outside of such settings.

BEST POSSIBLE COPY

Alternate Trade Name

Sponsor's comments

5. On February 21, 2001, Ligand submitted for Agency review an alternate trade name, ———. This name was developed with the assistance of ———. An Executive Summary of the development and research results of ——— published by ——— was included in this submission.

Does the Agency agree that ——— can be considered an appropriate trade name for the product? Please explain the rationale supporting the response.

OPDRA's comments

Please refer to ——— proprietary name consult conducted by OPDRA.

APPEARS THIS WAY
APPEARS THIS WAY
ON ORIGINAL

III. RECOMMENDATIONS

The analysis submitted in support of the Avinza proprietary name was not persuasive to minimize the Agency's concern with regard to potential medication errors. OPDRA does not recommend the use of the proprietary name "Avinza".

If you have any questions concerning this review please contact Sammie Beam at 301-827-3231.

Alina R. Mahmud, R.Ph.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

**APPEARS THIS WAY
ON ORIGINAL**

/s/

Alina Mahmud
3/27/01 09:26:32 AM
PHARMACIST

Jerry Phillips
3/27/01 10:35:32 AM
DIRECTOR

Martin Himmel
3/29/01 03:23:14 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: February 23, 2001

DUE DATE:
March 29, 2001

OPDRA CONSULT #: 01-0049

TO: Cynthia McCormick, MD
Director, Division of Anesthetics, Critical Care, and Addiction Drug Products
HFD-170

THROUGH: Kim Compton, Project Manager
HFD-170

PRODUCT NAME:

(Morphine sulfate extended-release)
Capsules
30 mg, 60 mg, 90 mg, 120 mg

NDA #: 21-260

Manufacturer: Elan Holdings, Inc.
Pharmaceutical Division

SAFETY EVALUATOR: Alina R. Mahmud, RPh.

SUMMARY: In response to a consult from the Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170), OPDRA conducted a review of the proposed proprietary name _____ to determine the potential for confusion with approved proprietary and generic names as well as pending names.

ODRA RECOMMENDATION: OPDRA does not recommend the use of the proprietary name _____

Jerry Phillips, R.Ph.
~~Associate Director for Medication Error Prevention~~
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

Martin Himmel, M.D.
~~Deputy Director~~
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY 1

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: March 14, 2001

NDA NUMBER: 21-260

NAME OF DRUG: _____
(Morphine sulfate extended-release) Capsules
30 mg, 60 mg, 90 mg, 120 mg

NDA HOLDER: Elan Holdings, Inc.

I. INTRODUCTION

This consult was written in response to a request from the Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170), for assessment of the tradename _____ regarding potential name confusion with other proprietary/generic drug names.

The sponsor has proposed _____ as a new tradename after the division recommended against the use of "Avinza". However, the sponsor still intends to appeal the recommendations against the name "Avinza" at the meeting scheduled for April 3, 2001. Labels and labeling were initially reviewed and commented on with the "Avinza" consult.

PRODUCT INFORMATION

_____ is the proposed proprietary name for morphine sulfate extended-release. _____ is formulated as a once-a-day capsule that contains both immediate release and extended release beads of morphine sulfate for oral administration. Each _____ capsule contains 30 mg, 60 mg, 90 mg, or 120 mg of morphine sulfate, USP. _____ is indicated for the relief of moderate to severe pain and is intended for the use in patients that require repeated dosing with opioid analgesics over periods of more than a few days. _____ will be available in both blister pack cartons and bottles of 30, 100, 250, 500 count.

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts^{iii,iii} as well as several FDA databases^{iv} for existing drug names which

ⁱ MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Co. Inc, 2000).

sound-alike or look-alike to ' — ' to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted^v. An Expert Panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies, to simulate the prescription ordering process.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name ' — '. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

Seven product names were identified in the Expert Panel Discussion that were thought to have potential for confusion with —. These products are listed in Table 1, along with the dosage forms available and usual FDA-approved dosage.

DDMAC did not have any concerns with the name in regard to promotional claims.

TABLE 1

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
	Morphine sulfate extended-release 30 mg, 60 mg, 90 mg, and 120 mg capsule (Rx)	Once-a-day dosing. Total daily dose depends on patient's tolerance and reaction to morphine.	
Albenza	Albendazole 200 mg tablet. (Rx)	400 mg twice daily with meals. Duration depends upon the parasitic infection being treated.	S/A, L/A per OPDRA
Evista	Raloxifene hydrochloride 60 mg tablet (Rx)	60 mg once daily	S/A, L/A per OPDRA
Aventyl	Nortriptyline hydrochloride 10 mg, 25 mg, and 10 mg/5ml (Rx)	Adults: 25 mg 3 or 4 times daily; begin at a low level and increase as required. The total daily dose can be given at bedtime. When doses > 100 mg/day are given, plasma levels of nortriptyline should be monitored and maintained in the optimum range of 50 to 150 ng/ml. Doses > 150 mg/day are not recommended.	S/A, L/A per OPDRA
Viagra	Sildenafil citrate 25mg, 50 mg, 100 mg tablet (Rx)	Recommended adult dose of 50 mg as needed; not to exceed 1 tablet per day. Dosage may be increased for a maximum dose of 100 mg.	S/A, L/A per OPDRA

ⁱⁱ American Drug index, 42nd Edition, 1999, Facts and Comparisons, St. Louis, MO.

ⁱⁱⁱ Facts and Comparisons, 2000, Facts and Comparisons, St. Louis, MO.

^{iv} COMIS, The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and online version of the FDA Orange Book.

^v WWW location <http://www.uspto.gov/tmdb/index.html>.

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
_____	Morphine sulfate extended-release 30 mg, 60 mg, 90 mg, and 120 mg capsule (Rx)	Once-a-day dosing. Total daily dose depends on patient's tolerance and reaction to morphine.	
Vincasar PFS	Vincristine sulfate 1 mg/mL injection (Rx)	Adults: 1.4 mg/m ² intravenously once a week	S/A, L/A per OPDRA
Vansil	Oxamniquine 250 mg capsule (Rx)	<i>Product has been discontinued</i>	S/A, L/A per OPDRA
Benza	Benzalkonium chloride 1:750 solution (otic)	Applied topically for skin antisepsis as needed	S/A, L/A per OPDRA
		*Frequently used, not all-inclusive.	**L/A (look-alike), S/A (sound-alike)

B. STUDY CONDUCTED BY OPDRA

1. Methodology

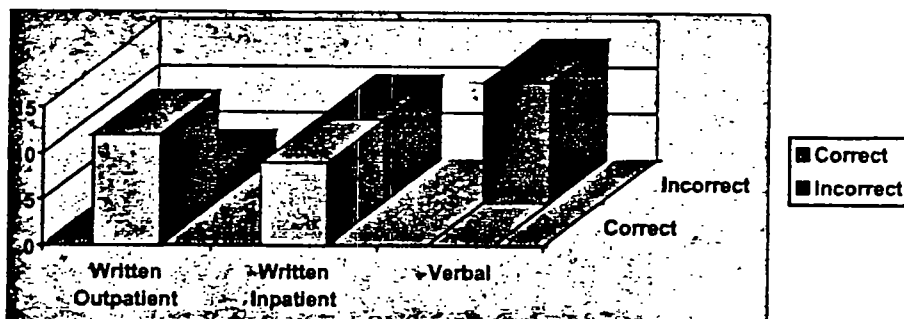
A separate study was conducted within FDA for the proposed proprietary name to determine the degree of confusion of _____ with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 86 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. An OPDRA staff member wrote an inpatient order and outpatient prescriptions, each consisting of a combination of marketed and unapproved drug products and prescriptions for _____ (see below). These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one OPDRA staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Outpatient: _____ 120 mg # 20 Sig: 1 QD	_____ 120 mg Take 1 capsule daily Dispense #20
Inpatient: _____ 120 mg QD	

2. Results

Results of these exercises are summarized below:

Study	No. of participants	# of responses (%)	response	Other response
Written: Outpatient	30	15 (50%)	12 (80%)	3 (20%)
Inpatient	28	18 (64%)	9 (50%)	9 (50%)
Verbal	28	13 (46%)	0 (0%)	13 (100%)
Total:	86	46 (53%)	21 (46%)	25 (54%)



Among participants in the two written prescription studies, 12 of 33 respondents (64%) interpreted the name incorrectly. The interpretations were misspelled variations of — such as *Venza*. One participant responded with *Vinga*, while *three participants interpreted the proposed name as Viagra*. Additionally, *one study participant noted the similarity in scripted appearance to Viagra*.

Among verbal prescription study participants, 13 out of 13 study participants (100%) interpreted the name incorrectly. Most of the incorrect name interpretations were phonetic variations of "—" such as *Vinsa*. Three study participants provided interpretations of the name with the vowel "a" as the first letter such as *Avensa*, *Avenza*, and *Advenca*. Furthermore, one study participant provided *Venzil* as an interpretation, which is strikingly similar to the approved drug product *Vansil*.

C. SAFETY EVALUATOR RISK ASSESSMENT

1. Look-alike and sound-alike names

In reviewing the proprietary name — the primary concerns raised were related to many sound-alike, look-alike names that already exist in the U.S. marketplace. Three products, Evista, Viagra, and Albenza were believed to be the most problematic in terms of medication error prevention.

OPDRA conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that — could be confused with Evista or Albenza. However, three participants from the *inpatient and outpatient* study responded with Viagra as an interpretation. Additionally, one person noted the similarity between — and Viagra. Although there are limitations to the predictive value of these studies primarily due to sample size, we have acquired safety concerns due to positive interpretations. A positive finding in a study with a small sample

size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population. Three participants from the verbal prescription analysis study provided interpretations with the vowel "a" as the first letter, such as Avenza, Avenza and Advenza. These interpretations are similar to the name Albenza which is an approved drug product.

Albenza is an orally administered broad-spectrum antihelmintic. It is indicated for the treatment of Neurocysticercosis and Hydatid disease caused by tapeworms. Albenza is available as a 200 mg tablet. A dose of 400 mg twice daily is recommended with the duration of therapy dependent on the disease being treated. Although _____ and Albenza do not look similar the names sound similar. Three participants from the verbal prescription study provided Avenza, Avenza and Advenza as an interpretation, all of which are similar to the name Albenza. Additionally, _____ and Albenza are solid oral dosage forms. A lack in visual similarity minimizes the potential for confusion, however a similarity in pronunciation can contribute to potential errors. Physicians in hospital settings often verbally request class II controlled substances directly from the narcotic cabinet positioned at the nurse's station (nurses are asked to supply physicians and/or inpatients with specified narcotics). Although _____ and Albenza do not share similar strengths and dosing frequencies, post-marketing experience has demonstrated errors occurring between drugs with only look-alike and/or sound-alike potential. The outcomes associated with the potential confusion of these two drugs are life-threatening. Fatalities associated with the use of Albenza have been reported due to granulocytopenia and pancytopenia, which results from harm inflicted to the liver or bone marrow. Additionally, acute renal failure related to Albenza therapy has been observed. A patient that receives _____ in place of Albenza, may experience respiratory depression and/or the possibility of an allergic reaction if the patient is hypersensitive to morphine.

Evista is a selective estrogen receptor modulator (SERM) with mixed estrogen agonist or antagonist (antiestrogen) activity in specific tissues. Evista is the proprietary name for Raloxifene. Evista is indicated in the prevention and treatment of osteoporosis in postmenopausal women with a dose indication of 60 mg once a day. _____ and Evista not only sound similar but also have the potential to look similar when scripted. Additionally, both share a similar strength, dosage form and once a day dosing frequency. As with Albenza, the potential for confusion is possible because physicians in hospitals often verbally request medications (including class II controlled substances) from nurses who have access to the narcotic cabinet positioned at the nurse's station. The risks associated with the inadvertent dispensing of _____ with Evista include all side effects and adverse events related to hormonal supplements. The risks associated with the inadvertent dispensing of Evista-for _____ include all side effects and adverse events related to central nervous system depression.

Viagra is the proprietary name for sildenafil citrate which is indicated for the treatment of erectile dysfunction. For most patients, the recommended dose is 50 mg taken, as needed, approximately 1 hour before sexual activity. Based on effectiveness and toleration, the dose may be increased to a maximum recommended dose of 100 mg or decreased to 25 mg. The maximum recommended dosing frequency is one tablet per day. Viagra is available in 25 mg, 50 mg and 100 mg tablets. Although Viagra and _____ do not sound similar, the names look strikingly similar when scripted (see writing sample below). **Three participants** from the **inpatient and outpatient** study responded with Viagra as an interpretation as another respondent noted the similarity in appearance. _____ and Viagra share similar dosing frequencies (once daily) and dosage forms. Despite the fact that _____ and Viagra do not share similar strengths, the potential for confusion is possible in that the strengths (60 mg and 50 mg, respectively) may appear similar when scripted (see writing sample

Virginia Slims [redacted] Comg
#10
TAD TAD TAD

Adderall	Inderal
Demerol	Desyrel
Codeine	Iodine
Codeine	Cardene
Codeine	Lodine
OxyContin	Oxybutynin

- ## Introduction

—'s study consisted of four phases, which utilized a cumulative total of 100 healthcare workers (50 pharmacists, 30 oncologists, 10 anesthesiologists, and 10 internal medicine specialists). The study concluded that ——— would not be confused with the drug names noted in the study since "there is little potential for prescribing/dispensing errors for ——— compared to the other drug names because of its specialized indication and limited distribution."

—'s report lacked information that would allow OPDRA to give a fair evaluation of —'s methodology of the study. Information on key methodological issues was not submitted by — such as the selection of the study sample of physicians and pharmacists, and the validation of the techniques used.

(a) Selection of Participating Practitioners

- According to the report, the participants were randomly selected across pre-selected geographic areas. However, the information on the process of how participating physicians and pharmacists were selected was not included in —'s report. The criteria on the selection process (inclusion and exclusion criteria) and how those criteria were met were not explained.
- The sampling frame for the selection of the participants was not given. For example, did the selection of cardiologists arise from a list of professional organizations? Without the information of the selection and recruitment process the results of this study cannot be interpreted and applied to the universe of practicing physicians and pharmacists in the United States, especially since the study sample was small.
- There was no mention of whether or not the participants were reimbursed for their participation in the study. Reimbursement may bias the results of the study.

(b) Validation of Methods Used

Information was not presented to demonstrate that the methods used in the study actually work in predicting whether any existing brand/generic names may be confusingly similar to the test name in actual practice.

- **Verbal Prescription Filling**

The methodology in the study is very different from an actual practice situation, in an actual practice setting where a very busy environment exists, pharmacists receive the entire prescription over the phone from a prescriber. The drug name is pronounced in the context of an entire prescription. Usually, once the pharmacist listens to all the information, the interpreted prescription is then re-read to the physician and clarifies any necessary information. Such clarification can result in the unveiling of an error in perception of the drug name. The method in the study, where only the name is spoken, is contrived and unrealistic. The result may have been very different had the simulation been more true to actual practice.

- **Scripted Prescription Filling**

~~As in the above comment regarding the Verbal Prescription Filling, the methodology is not clearly described or validated in this portion of the study report. According to —'s report, the physicians scripted the product name, and the script was sent on-line for the pharmacists' interpretation. This method does not simulate actual prescription practice and the results cannot be generalized to an actual practice situation.~~

- **Orthographic String Similarity Testing**

The results have not been validated or related to real outcomes. Nothing is included about the potential severity of outcome that could be associated with a mix up in the list of parameters that are related to patient safety.

- **Use of "positive" and "negative" controls**

forms. A lack in visual similarity minimizes the potential for confusion however a similarity in pronunciation can contribute to potential errors. Physicians in hospital settings often verbally request class II controlled substances directly from the narcotic cabinet positioned at the nurse's station (nurses are asked to supply physicians and/or patients with specified narcotics). Although _____ and Albenza do not share similar strengths and dosing frequencies, post-marketing experience has demonstrated errors occurring between drugs with only look-alike and/or sound-alike potential. The outcomes associated with the potential confusion of these two drugs are life-threatening. Fatalities associated with the use of Albenza have been reported due to granulocytopenia and pancytopenia, which results from harm inflicted to the liver or bone marrow. Additionally, Acute renal failure related to Albenza therapy has been observed. A patient that receives _____ in place of Albenza, may experience respiratory depression and/or the possibility of an allergic reaction if the patient is hypersensitive to morphine.

_____ and Evista not only sound similar but also have the potential to look similar when scripted. Additionally, both share a similar strength, dosage form and once a day dosing frequency. As with Albenza, the potential for confusion is possible because physicians in hospitals often verbally request medications (including class II controlled substances) from nurses who have access to the narcotic cabinet positioned at the nurse's station. The risks associated with the inadvertent dispensing of _____ with Evista include all side effects and adverse events related to hormonal supplements. The risks associated with the inadvertent dispensing of Evista for _____ include all side effects and adverse events related to central nervous system depression.

Although Viagra and _____ do not sound similar, the names look strikingly similar when scripted (see writing sample below). *Three participants* from the *inpatient and outpatient* study responded with Viagra as an interpretation as another respondent noted the similarity in appearance. _____ and Viagra share similar dosing frequencies (once daily) and dosage forms. Despite the fact that _____ and Viagra do not share similar strengths, the potential for confusion is possible in that the strengths (60 mg and 50 mg, respectively) may appear similar when scripted (see writing sample below). Post-marketing experience has demonstrated errors occurring between drugs that share look-alike and sound-alike properties solely. The inadvertent confusion of _____ for Viagra could cause central nervous depression and/or the possibility of an allergic reaction if the patient is hypersensitive to morphine. The risk associated with the inadvertent confusion of Viagra for _____ include all side effects and adverse events related to Viagra. Also, the patient will remain untreated

**APPEARS THIS WAY
ON ORIGINAL**

BEST POSSIBLE COPY

for moderate to severe pain.

Handwritten notes:
[] Comp
#10
T Q D T Q D

In, addition, post-marketing experience has demonstrated errors occurring between Class II controlled substances and non-scheduled drug products. Such examples include:

Adderall	Inderal
Demerol	Desyrel
Codeine	Iodine
Codeine	Cardene
Codeine	Lodine
OxyContin	Oxybutynin

2. _____ (Confidential and proprietary and should not be noted for FOI purposes)

Introduction

_____ was contacted by the sponsor to conduct a study to identify potential sound-alike and look-alike existing drug names to _____. The purpose of this study was to "identify confusion issues between _____ and existing brand names or generic names, and to assess the potential for patient harm."

_____’s study consisted of four phases, which utilized a cumulative total of 100 healthcare workers (50 pharmacists, 30 oncologists, 10 anesthesiologists, and 10 internal medicine specialists). The study concluded that "_____" would not be confused with the drug names noted in the study since "there is little potential for prescribing/dispensing errors for _____ compared to the other drug names because of its specialized indication and limited distribution."

Review

_____’s report lacked information that would allow OPDRA to give a fair evaluation of _____’s methodology of the study. Information on key methodological issues was not submitted by _____ such as the selection of the study sample of physicians and pharmacists, and the validation of the techniques used.

(a) Selection of Participating Practitioners

- According to the report, the participants were randomly selected across pre-selected geographic areas. However, the information on the process of how participating physicians and pharmacists were selected was not included in _____’s report. The criteria on the selection process (inclusion and exclusion criteria) and how those criteria were met were not explained.

- The sampling frame for the selection of the participants was not given. For example, did the selection of cardiologists arise from a list of professional organizations? Without the information of the selection and recruitment process the results of this study cannot be interpreted and applied to the universe of practicing physicians and pharmacists in the United States, especially since the study sample was small.
- There was no mention of whether or not the participants were reimbursed for their participation in the study. Reimbursement may bias the results of the study.

(b) Validation of Methods Used

Information was not presented to demonstrate that the methods used in the study actually work in predicting whether any existing brand/generic names may be confusingly similar to the test name in actual practice.

- **Verbal Prescription Filling**

The methodology in the study is very different from an actual practice situation, in an actual practice setting where a very busy environment exists, pharmacists receive the entire prescription over the phone from a prescriber. The drug name is pronounced in the context of an entire prescription. Usually, once the pharmacist listens to all the information, the interpreted prescription is then re-read to the physician and clarifies any necessary information. Such clarification can result in the unveiling of an error in perception of the drug name. The method in the study, where only the name is spoken, is contrived and unrealistic. The result may have been very different had the simulation been more true to actual practice.

- **Scripted Prescription Filling**

As in the above comment regarding the Verbal Prescription Filling, the methodology is not clearly described or validated in this portion of the study report. According to —s report, the physicians scripted the product name, and the script was sent on-line for the pharmacists' interpretation. This method does not simulate actual prescription practice and the results cannot be generalized to an actual practice situation.

- **Orthographic String Similarity Testing**

The results have not been validated or related to real outcomes. Nothing is included about the ~~potential severity of outcome that could be associated with a mix up in the list of parameters that~~ are related to patient safety.

- **Use of "positive" and "negative" controls**

—s report stated repeatedly that "positive" and "negative" controls for — were used in several analyses, but it is unclear what it was meant by it. The use of the terms in the analyses presented in this report appears to be incorrect.

- **BRANDTEST** —

— completed an additional phase to further evaluate the accuracy of verbal and written similarity between Avinza and Albenza, Alfenta, Aventyl and Evista. The participants (30 oncologists, 10

(anesthesiologists, 10 internal medicine specialists and 50 pharmacists) were instructed to listen to a recording of — and/or view a scripted representation of —. The participants reported what they heard or viewed by selecting one name from a list of test drug names one of which was —. Although it was not mentioned how many prescriptions were allocated to each pharmacist, it is highly possible that after the first prescription, the pharmacist would guess the purpose of the study and select the right drug.

Overall, the study conducted by — lacks information to assess the validity of the study. The sample size is too small to detect all the potential drug names at risk for being confused with —.

**APPEARS THIS WAY
ON ORIGINAL**

V. RECOMMENDATIONS

OPDRA does not recommend the use of the proprietary name "_____".

OPDRA would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam, R.Ph. at 301-827-3231.

Alina R. Mahmud, R.Ph.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

**APPEARS THIS WAY
ON ORIGINAL**

/s/

Alina Mahmud
3/26/01 02:40:09 PM
PHARMACIST

Jerry Phillips
3/27/01 09:21:13 AM
DIRECTOR

Martin Himmel
3/29/01 03:06:36 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION		
TO (Division/Office): OPDRA, HFD-400, (15B-03) ammie Beam, Project Manager			FROM: HFD-170 (Division of Anesthetic, Critical Care, and Addiction Drug Products), Kim Compton, Project Manager		
DATE 2/21/01	IND NO.	NDA NO. 21-260	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT 2/21/01	
NAME OF DRUG (morphine sulfate)		PRIORITY CONSIDERATION High	CLASSIFICATION OF DRUG 3S	DESIRED COMPLETION DATE 3/21/01	
NAME OF FIRM: Elan Pharmaceuticals					
REASON FOR REQUEST					
I. GENERAL					
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY		<input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT		<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):	
II. BIOMETRICS					
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):			<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS					
<input type="checkbox"/> DISSOLUTION <input checked="" type="checkbox"/> BIOAVAILABILITY STUDIES PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE					
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS					
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: Please review the trademark name for this drug. They have proposed a new tradename of _____ after we recommended against the use of "Avinza" and " _____ ". The sponsor has requested "expeditious review" citing the pending action date for the NDA (March 30, 2001).					
*NOTE: The sponsor still intends to appeal the recommendation against the name "Avinza" at the meeting scheduled for April 3, 2001.					
If you have any questions, please contact Kim Compton, Regulatory Project Manager, at 301-827-7432. Thank you for your assistance.					
Cc: Aleta Crane, HFD-170					
SIGNATURE OF REQUESTER Kimberly Compton, HFD-170			METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER		

BEST POSSIBLE COPY

/s/

Kimberly Compton

2/23/01 01:20:32 PM

APPEARS THIS WAY
ON ORIGINAL

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: October 2, 2000

DUE DATE:

December 14, 2000

OPDRA CONSULT #: 00-0264

TO: Cynthia McCormick, MD
Director, Division of Anesthetics, Critical Care, and Addiction Drug Products
HFD-170

THROUGH: Kim Compton, Project Manager
HFD-170

PRODUCT NAME:

Avinza
(Morphine sulfate)
Rapid Onset Extended Release (ROER)
Capsules
30 mg, 60 mg, 90 mg, 120 mg

Manufacturer: Elan Holdings, Inc.
Pharmaceutical Division

NDA #: 21-260

SAFETY EVALUATOR: Alina R. Mahmud, RPh.

SUMMARY: In response to a consult from the Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170), OPDRA conducted a review of the proposed proprietary name "Avinza" to determine the potential for confusion with approved proprietary and generic names as well as pending names.

ODRA RECOMMENDATION: OPDRA does not recommend the use of the proprietary name "Avinza".

Jerry Phillips, R.Ph.

Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

Martin Himmel, M.D.

Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

APPEARS THIS WAY
ON ORIGINAL

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: November 30, 2000

NDA NUMBER: 21-260

NAME OF DRUG: Avinza
(Morphine Sulfate)
Extended Release Capsules
30 mg, 60 mg, 90 mg, 120 mg

NDA HOLDER: Elan Holdings, Inc.

I. INTRODUCTION

This consult was written in response to a request from the Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170), for assessment of the tradename "Avinza", regarding potential name confusion with other proprietary/generic drug names.

PRODUCT INFORMATION

Avinza is the proposed proprietary name for morphine sulfate. Avinza is formulated as a once-a-day Extended Release capsule that contains both immediate release and extended release beads of morphine sulfate for oral administration. Each Avinza capsule contains 30 mg, 60 mg, 90 mg, or 120 mg of morphine sulfate, USP. Avinza is indicated for the relief of moderate to severe pain and is intended for the use in patients that require repeated dosing with opioid analgesics over periods of more than a few days. Avinza will be available as a capsule in both blister pack cartons and bottles of 30, 100, 250, 500 counts.

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts^{i,ii,iii} as well as several FDA databases^{iv} for existing drug names which

ⁱ MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Co. Inc, 2000).

ⁱⁱ American Drug index, 42nd Edition, 1999, Facts and Comparisons, St. Louis, MO.

ⁱⁱⁱ Facts and Comparisons, 2000, Facts and Comparisons, St. Louis, MO.

^{iv} COMIS, The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and online version of the FDA Orange Book.

sound-alike or look-alike to "Avinza" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted^v. An Expert Panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies, to simulate the prescription ordering process.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name "Avinza". Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

Ten product names were identified in the Expert Panel Discussion that were thought to have potential for confusion with Avinza. These products are listed in Table 1, along with the dosage forms available and usual FDA-approved dosage.

DDMAC did have concerns with the _____ Extended Release _____ portion of the name, as it is believed to be promotional in tone. ✓

TABLE 1

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
Avinza	Morphine Sulfate _____ capsule. Available in 30 mg, 60 mg, 90 mg, and 120 mg.	Once-a-day dosing. Total daily dose depends on patient's tolerance and reaction to morphine.	
Albenza	Albendazole 200 mg tablet. (Rx)	400 mg twice daily with meals. Duration depends upon the parasitic infection being treated.	S/A, L/A per OPDRA
Alfenta	Alfentanil 500 mcg/mL (Rx)	Initial dose: 8-50 mcg/kg, followed by a maintenance dose of 0.3-15 mcg/kg.	S/A, L/A per OPDRA
Evista	Raloxifene hydrochloride 60 mg tablet (Rx)	60 mg once daily	S/A, L/A per OPDRA
Aventyl	Nortriptyline hydrochloride 10 mg, 25 mg, and 10 mg/5ml	Adults: 25 mg 3 or 4 times daily; begin at a low level and increase as required. The total daily dose can be given at bedtime. When doses > 100 mg/day are given, plasma levels of nortriptyline should be monitored and maintained in the optimum range of 50 to 150 ng/ml. Doses > 150 mg/day are not recommended.	S/A, L/A per OPDRA

^v WWW location <http://www.uspto.gov/tmdb/index.html>.

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
Avinza	Morphine Sulfate — capsule. Available in 30 mg, 60 mg, 90 mg, and 120 mg.	Once-a-day dosing. Total daily dose depends on patient's tolerance and reaction to morphine.	
Avandia	Rosiglitazone 2 mg, 4 mg, and 8 mg tablet (Rx)	Maximum dose of 8 mg/day	S/A, L/A per OPDRA
Relenza	Zanamavir Rotodisks (Rx)	Two inhalations twice daily for 5 days	S/A, L/A per OPDRA
Avita	Tretinoin 0.025% topical cream. (Rx)	Apply at bedtime.	S/A, L/A per OPDRA
Aviane ***	Levonorgestrel and estradiol tablets, 0.1 mg/ 0.02 mg (ANDA) ***	One tablet daily. 21 or 28 day regimens.	L/A per OPDRA
_____	_____ ***	Strength and dosing frequency not listed	L/A, S/A per OPDRA
Avinar	Uredepa	Antineoplastic agent Currently not marketed Listed in widely used and accessible reference texts.	L/A per OPDRA
		*Frequently used, not all-inclusive.	**L/A (look-alike), S/A (sound-alike)

***NOTE: This review contains proprietary and confidential information that should not be released to the public. ***

B. STUDY CONDUCTED BY OPDRA

1. Methodology

A separate study was conducted within FDA for the proposed proprietary name to determine the degree of confusion of Avinza with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 89 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. An OPDRA staff member wrote an inpatient order and outpatient prescriptions, each consisting of a combination of marketed and unapproved drug products and prescriptions for Avinza (see below). These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one OPDRA staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

HANDWRITTEN PRESCRIPTIONS

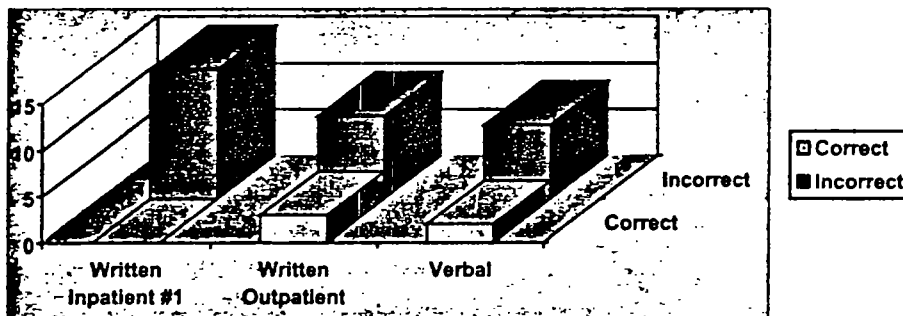
VERBAL PRESCRIPTION

Outpatient: Avinza 30 mg # 20 Sig: 1 QD	Avinza 30 mg Take 1 capsule daily Dispense #20
Inpatient: Avinza 30 mg QD	

2. Results

Results of these exercises are summarized below:

Study	No. of participants	# of responses (%)	"Avinza" response	Other response
Written: Outpatient	31	12 (39%)	3 (25%)	9 (75%)
Inpatient	29	14 (48%)	0 (0%)	14 (100%)
Verbal: Outpatient	29	10 (35%)	2 (20%)	8 (80%)
Total:	89	36 (40%)	5 (14%)	31 (86%)



Among participants in the written prescription studies, 23 of 26 respondents (88%) interpreted the name incorrectly. The interpretations were misspelled variations of "Avinza". Eight participants interpreted the second vowel in Avinza as an "e". Two participants from the inpatient study analysis interpreted the name as *Arinza*. Interpretations included: *Avenza*,

Orenza, *Avunza*, *Cevenza*, *Arinzec*, *Arinox*, *Arinze*, *Azinex*, *Aringer*, *Arineze*, *Arinyc*, and *Arinzc*.

Among verbal prescription study participants, 8 of 10 (80%) of the study participants interpreted the name incorrectly. Most of the incorrect name interpretations were phonetic variations of "Avinza". Six study participants interpreted the second vowel "i" as an "e". Three participants interpreted the ending syllable "za" as "da", "ta", and "sa". Interpretations included *Aventa*, *Avenda*, *Avensa*, *Avenza*, *Avineza*, and *Arinza*.

C. SAFETY EVALUATOR RISK ASSESSMENT

and Alfenta could possibly share the same total daily dose because the dose for Alfenta is calculated based on weight. Furthermore, the use of Avinza is appropriate in a hospital setting, which is similar to the practice setting of Alfenta. If Alfenta is inadvertently confused for Avinza, the drug interaction profile of Alfenta poses significant risks for a patient. Drug-Drug interactions with Alfenta include itraconazole, diltiazem, naltrexone, rifabutin, betablockers, ondansetron, and macrolide antibiotics. These drug interactions expose a patient to serious and possibly life-threatening adverse events.

⇒Evista is a selective estrogen receptor modulator (SERM) with mixed estrogen agonist or antagonist (antiestrogen) activity in specific tissues. Evista is the proprietary name for Raloxifene. Evista is indicated in the prevention and treatment of osteoporosis in postmenopausal women with a dose indication of 60 mg once a day. Avinza and Evista not only sound similar but also look similar when scripted, both containing six characters. Additionally, both share similar dosage strengths, dosage forms and once a day dosing frequency. The risks associated with the inadvertent dispensing of Avinza with Evista include all side effects and adverse events related to hormonal supplements. The risks associated with the inadvertent dispensing of Evista for Avinza include all side effects and adverse events related to central nervous system depression.

⇒Aventyl is a tricyclic antidepressant and is the proprietary name for nortriptyline. The manufacturers state that the usual adult dosage of nortriptyline is 75-100 mg daily. Although nortriptyline has been administered in up to 4 divided doses throughout the day, it is long-acting and the entire daily dose may be administered at one time. Avinza is also recommended as a once daily dose. In addition, Avinza and Aventyl sound similar and also look similar. As demonstrated by the verbal study analysis conducted by OPDRA, one participant interpreted Avinza as Aventa, which is similar to Aventyl. If these drugs were inadvertently dispensed, a patient could experience the side effects of CNS depression with Avinza or side effects associated with Aventyl.

Other drug names that have low potential for name confusion with Avinza include: Relenza, ~~Aviane***~~, Avandia, and Avinar. These drugs either sound similar or look similar to Avinza.

- Relenza Rotodisk is an inhaler preparation approved for the treatment of influenza A and B.
- Three study participants from the written inpatient and voice mail studies interpreted Avinza as Arinza. Arinza looks and sounds similar to ~~Aviane~~ which has an active IND pending.
- An active ANDA for Aviane is currently under review with an unknown approval date.
- Avandia is an antidiabetic agent indicated for Type II Diabetes.
- Avinar is an antineoplastic agent listed in one of the widely used and easily accessible reference text, however, this drug product is not currently marketed in the United States.

*****NOTE: This review contains proprietary and confidential information that should not be released to the public. *****

2. ~~Aviane~~ as part of the established name

~~Aviane~~ Extended Release capsule contains both immediate release and extended release beads of morphine sulfate for oral administration. As per Dan Boring of the USAN council, the classification of the capsule formulation as a ~~Aviane~~ Extended Release is not recommended as part of the established name. Most pelletized formulations, including the ~~Aviane~~ capsule, for extended release have a fraction of the dose delivered

immediately with a larger amount released at later intervals. The *extended release* dosage descriptor is adequate alone to classify Avinza's formulation because the immediate release aspect could be viewed as a subset of the extended release characteristics.

3. _____

The applicant, Elan Pharmaceuticals, requested _____ to evaluate the proposed proprietary name, Avinza, for potential confusion with existing sound-alike and look-alike names and the potential for patient harm that could result from the identified confusion. The _____ study was reviewed and commented on by Judy Staffa, Ph.D, R.Ph, an epidemiologist within OPDRA. Dr. Staffa concluded that the study does not provide sufficient information on its methodology to allow for assessment of appropriateness (see Appendix A for full review).

Dr. Staffa's evaluation of the _____ study also concluded that the risks associated with the potential confusion among Avinza and Evista or Relenza are significantly high, such as 3% and 1% respectively. A positive finding in a study with small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population. The _____ findings support our findings in that the potential for confusion among these drug products does exist.

III. LABELING, PACKAGING AND SAFETY RELATED ISSUES

In the review of the draft container label and draft package insert for Avinza, OPDRA has attempted to focus on safety issues relating to possible medication errors. We have identified several areas of possible improvement, in the interest of minimizing potential user error.

A. ALL CONTAINER LABELS

1. Front Panel

- a. The controlled substance symbol shall be more prominent per 21 CFR 1302.04.
- b. We recommend increasing the prominence of the proprietary name and established name.
- c. We recommend relocating the net quantity statement so it does not appear in conjunction with the product strength. This will prevent the confusion of the net quantity with the product strength.
- c. We recommend differentiating the various strengths by using boxing, contrasting colors or by some other means.
- d. Revise the established name to read: Morphine Sulfate Extended-release Capsules.
Note: Delete _____ and _____

2. Side Panel

- a. We recommend organizing the information on the side panel by _____ (i.e. one or both logos and Ligand and Elan Part Number) to the package insert. This will allow the practitioner to easily locate information on the side panel.
- b. We recommend relocating the phone number for medical information to appear in the package insert rather on the side panel of the label to prevent cluttering.
- c. Please note that the statement "WARNING: MAY BE HABIT FORMING" is no longer required as a result of the 1997 FDA Modernization Act.
- d. There is no reason to bring such prominence (bold and all capital letters) to the note about dispensing in a tight container. In fact, this appears as the most prominent information on the label.

B. ALL BLISTER PACK CARTONS

See comments under All Container Labels, as appropriate.

C. ALL BLISTER CARDS

See comments under All Container Labels, as appropriate.

**APPEARS THIS WAY
ON ORIGINAL**

IV. RECOMMENDATIONS

1. OPDRA does not recommend the use of the proprietary name "Avinza".
2. OPDRA has recommended some labeling interventions that might minimize user error.

OPDRA would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam, R.Ph. at 301-827-3161.

Alina R. Mahmud, R.Ph.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

**APPEARS THIS WAY
ON ORIGINAL**

cc: NDA

HFD-170; Division files; Kim Compton, Project Manager

HFD-170; Cynthia McCormick, Director, DACADP

HFD-400; Jerry Phillips, Associate Director, OPDRA

Electronic only cc:

HFD-400; Peter Honig, Director, OPDRA

HFD-440; Mary Dempsey, Project Manager, OPDRA

HFD-440; Judy Staffa, Epidemiologist, OPDRA

HFD-530; Dan Boring, USAN council

HFD-040; Patricia Staub, Senior Regulatory Review Officer, DDMAC

HFD-400; Sammie Beam, Project Manager, OPDRA

L:\OPDRA00\MAHMUD\00-0264\VINZA.FIN.DOC

**APPEARS THIS WAY
ON ORIGINAL**

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION	
TO (Division/Office): OPDRA, HFD-400, (15B-33) Peter Honig, M.D.			FROM: HFD-170 (Division of Anesthetic, Critical Care, and Addiction Drug Products), Dr. Cynthia McCormick	
DATE 9/20	IND NO.	NDA NO. 21-260	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT May 25, 2000
NAME OF DRUG Avinza (morphine sulfate)		PRIORITY CONSIDERATION High	CLASSIFICATION OF DRUG 3S	DESIRED COMPLETION DATE 11/24/2000
NAME OF FIRM: Elan Pharmaceuticals (co-marketed by Ligand Pharmaceuticals Inc.-which will handle the correspondence with the Agency)				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> PAPER NDA <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> CONTROL SUPPLEMENT <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH	
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):			<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):	
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST	
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS	
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL	
COMMENTS/SPECIAL INSTRUCTIONS: Please review the trademark name for this drug. We submitted a consult to you on September 19, 2000 for the tradename _____ However, Elan Pharmaceuticals is submitting a new trade name, Avinza for the drug product previously identified as _____. Please disregard the previous consult of September 19, 2000 If you have any questions, please contact Sara Shepherd, Regulatory Project Manager, at 301-827-7430. Thank you for your assistance.				
SIGNATURE OF REQUESTER			METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> HAND	
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER	

BEST POSSIBLE COPY